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Associations between ventricular size and diffusivity in patients with post-acute traumatic brain injury; a diffusion tensor tractography study

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Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique, which provides information about the integrity and arrangement of white matter (WM) fibers. DTI is used to examine white matter pathology and to show abnormalities not seen in conventional MRI traumatic brain injury (TBI) patients.

Although DTI parameters generally correlate with white matter integrity, in some tracts they have been suggested to be influenced by ventricular enlargement. This effect, which is probably due to stretching, straightening or compression of fibers, can be reverse to that reported in injury. Cingulum is a major WM tract close to the lateral ventricles and is likely to be prone to the influence of ventricular size. Correlations between ventricular size and DTI parameters of normal cingulum have been reported recently. Central atrophy causing ventricular enlargement is often seen after TBI. Our aim was to evaluate associations between the size of lateral ventricles and DTI parameters of cingulum in patients with TBI. The study included 157 subjects: 80 healthy controls, 40 patients with mild TBI and 37 patients with moderate or severe TBI. DTI parameters were correlated with corresponding cross sectional areas of lateral ventricles.

Different from the findings in healthy controls, DTI parameters in cingulum generally did not correlate with ventricular size in patients with TBI. This may be due to the coexistent but opposite effects of ventricular enlargement and traumatic axonal injury on diffusion parameters. This phenomenon may mask abnormalities when using DTI in patients with TBI.

Keywords: Diffusion tensor imaging, diffusion tensor tractography, cingulum, traumatic brain injury

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1 Abstract

Purpose To evaluate if diffusion parameters in the cingulum of patients with post-acute traumatic brain injury (TBI) are associated with the size of the lateral ventricles.

Methods MRI at 3T including diffusion tensor imaging (DTI) was performed for 80 normal subjects (19-56 years) and 77 patients with TBI (18-56 years, 40 with mild and 37 with moderate-to-severe TBI). Mean diffusivity (MD) and fractional anisotropy (FA) were measured by tractography at a FA threshold of 0.30. Additionally, core MD, FA, axial diffusivity (AD) and radial diffusivity (RD) were analyzed using tractography-based core analysis in a volume of 3.0 cm^3. The parameters were correlated with corresponding cross-sectional coronal areas of lateral ventricles (ALV).

Results In patients with TBI, ALVs were larger than in controls. Of the DTI parameters, there were significant differences only in core FA and RD values between patients and controls. In controls, ALVs correlated positively with tract volumes (r=0.33) and core FAs (r=0.29) and negatively with MDs (r=-0.29), core MDs (r=-0.36) and RDs (r=-0.34) of the cingulum. In patients with mild TBI, the volumes of cingulum correlated positively (r=0.35) with ALV. Other DTI parameters did not correlate with the ALV in the patient groups.

Conclusion In patients with TBI, DTI parameters of the cingulum generally do not correlate with ventricular size, as they do in normal controls. This can be due to the coexisting but conflicting effects of traumatic axonal injury and ventricular enlargement on diffusion. This phenomenon may mask abnormalities when using DTI to detect abnormalities of the cingulum in patients with TBI.

Keywords Diffusion tensor imaging – Diffusion tensor tractography – Cingulum – Traumatic brain injury

2 Introduction

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique to model the three-dimensional spatial distribution of water diffusion in each voxel [1]. DTI is capable of characterizing white matter architecture and provides clinically useful information about the integrity and arrangement of white matter fibers of the brain [2–4]. Of the DTI parameters

axial diffusivity (AD) has been shown to be associated with the amount and structure of axons and radial diffusivity (RD) with myelin content [5–10]. Thus, the clinically most commonly used parameters fractional anisotropy (FA) and mean diffusivity (MD) are highly sensitive to the microstructural integrity of WM fibers and can be used to show changes not visible on conventional images. However, the parameters are not specific to any histopathological change [11].

One of the most promising areas to apply DTI to the clinics is to assess the presence of diffuse axonal injury (DAI) in patients with TBI. DAI is believed to be a major contributor to cognitive dysfunction in patients with TBI [12–17]. Conventional computed tomography (CT) and MRI are either unable to detect or considerably underestimate the distribution and severity of DAI. DTI is often capable in detecting DAI in patients without abnormalities in CT or conventional MRI [18–22]. Reduced FA in several areas of the brain are reported in patients with all severities of TBI in post-acute phase [20, 21, 23–28]. After TBI, also increased MD and RD have been reported in several studies [20, 23–26], and changes in AD in some studies [24, 27].

Factors not related to the structure and amounts of axons and myelin, like compression, stretching or straightening of fibers, can also influence DTI parameters. Increased FA and AD of the corticospinal tract has been reported in hydrocephalus, assumed to be due to mechanical compression or stretching of the tract [29–31]. The cingulum has a long course around the lateral ventricles, why it might be especially prone to the influence of the ventricular size. Recently, ventricular enlargement was reported to be associated with decreased RD and MD and increased FA in the core of the cingulum in normal middle-aged subjects [32]. Central atrophy causing ventricular enlargement is commonly seen after a TBI [33–35]. Thus, DTI parameters of the cingulum in TBI could be influenced, in addition to DAI, also by ventricular enlargement. The findings in normal cingulum suggest that this effect might decrease the likelihood of finding TBI-related alterations in DTI parameters. In the current study, our purpose was to evaluate the relationship between the size of the lateral ventricles and diffusivity of the cingulum in patients with post-acute TBI compared to controls.

3. Materials and methods

3.1 Patients

Local ethical committee approval and informed consent were obtained. The study subjects comprised 157 people: 80 healthy subjects (aged 19-56, mean 36.6 ± 10.9 years; 40 men and 40 women), 40 patients with mild TBI (aged 19-54, mean 37.3 ± 10.4 years; 20 men and 20 women) and 37 patients with moderate or severe TBI (aged 18-56, mean 39.1 ± 10.1 years; 18 men and 19 women).

A questionnaire and medical records were used in selecting the control subjects. Exclusion criteria were as follows: earlier TBI, other neurological diseases, and hypertension. In addition, subjects with multiple T2-hyperintensities (>5mm) or other MRI abnormalities were excluded.

Inclusion criteria for the TBI group were (1) TBI with a loss of consciousness and/or posttraumatic amnesia (PTA); (2) no other neurological, psychiatric or vascular diseases that could possibly affect brain structure, no chronic hypertension or alcoholism; (3) normal routine MRI; (4) time from TBI more than 3 months.

Severity of TBI was clinically determined based on both Glasgow Coma Scale (GCS) and duration of PTA, as follows: GCS 13-15 and PTA <24h =mild TBI; GCS 9-12 and/or PTA 1-7 days =moderate TBI; GCS 3-8 and/or PTA 1-4 weeks =severe TBI. The extended Glasgow Outcome Scale (GOS-E) was used to evaluate the outcome. Thorough neurological and neuropscyhological examinations were conducted for all patients. The demographic data of the study subjects are presented in Table 1.

3.2 MR imaging

The study subjects underwent 3T MRI (Achieva, Philips Medical Systems, Best, the Netherlands) equipped with an eight-channel transmit-receive head coil. The imaging protocol consisted of DTI images of transverse T2-weighed turbo spin echo images, coronal fluid attenuated inversion recovery (FLAIR) images and sagittal 3DT1 turbo field echo images.

For the transverse DTI images, the following parameters were used: diffusion-weighted turbo spin echo EPI images (TR/TE 5877/62, 65 slices with 2.0-mm thickness, gap 0.0 mm,

112 × 128-r matrix, turbo factor 59, EPI factor 59, FOV 224 mm, RFOV 100%, number of excitations 2, imaging time 4 min 11 s), b values of 0 and 800 s/mm2, and 15 different gradient encoding directions were used; the images had 2.0 × 2.0 × 2.0-mm voxel size.

All transverse images were obtained according to the line between the lower border between the genu and splenium of the corpus callosum (CC). DTI images were disapproved and the sequence was repeated, if any head movement was detected in the image series.

Post-processing with a diffusion registration tool was performed to remove distortions and misalignments due to shear and eddy currents and head motion.

3.3 Image analysis and tractography

Deterministic DTI tractography (DTT) (FiberTrak package, Philips) was performed by using free-hand region-of-interest (ROI) -based approach. Two inclusion ROIs were placed in standard positions on the coronal images of the color-coded map. They were manually drawn around the cingulum using the superoposterior border of aqueduct and anterior commissure as anatomical landmarks. In addition, the fibers of CC were eliminated by using an exclusion ROI at the midline [36].

Fiber tracking of the cingulum was performed using FA threshold 0.30 and a direction threshold <27°. Tractography-based core analysis (TBCA) was then achieved by changing the FA threshold gradually until the volume of 3cm^3 [36].

The measurements included FA, MD and main diffusion eigenvectors (λ_1, λ_2, and λ_3).

The cross-sectional areas of the lateral ventricles were measured by using the reconstructions of 3DT1 images. Coronal reconstructions of the 3DT1 images perpendicular to the line between the lower border of the genu and splenium of corpus callosum were used for measurement of the area of the lateral ventricles. The area of the body of each lateral ventricle was measured at the midline between anterior border of genu and posterior border of splenium.

3.4 Statistical methods

Student´s t test with Bonferroni correction was used for comparisons between patients and controls. Pearson correlation coefficients were calculated to study associations between

ventricle size and volumes, $FA_{0.30}$, $MD_{0.30}$, FAC, MDC, AD and RD of cingulum. In these analyses, the patients were divided into mild TBI and moderate to severe TBI groups, and the results of the right and left side were combined.

Linear models were built up for $FA_{0.30}$, $MD_{0.30}$, FAC, MDC, AD and RD so that explanatory variables in the models were age (as classified), ventricle size (log-transformed data), gender, group (TBI/normal), side(right/left), and interaction of ventricle size and group.

All statistical tests were performed as two-sided, with a significance level set at 0.05. The analyses were performed using SAS software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

4 Results

The reproducibility of the technique is published previously using identical MRI and analysis methods [36]. Group demographics are shown in Table 1. There were no significant differences in demographic parameters between the control subjects and patients with TBI.

The results are shown in Tables 2,3 and Fig 1 A-D. When comparing the DTI parameters between the controls and the patients, several significant p values were found (Table 2). After Bonferroni correction only the difference of FAC (p=0.002) and RD (p=0.0034) of the right cingulum was significant. Further, the ALVs differed both on right (p=0.0001) and left (p=0.001) side between patients and controls.

In controls, ALV correlated positively with volume (r=0.33, p<0.0001) and FAC (r=0.29, p=0.0002) and negatively with MD (r=-0.29, p=0.0003), MDC (r=-0.36, p<0.0001) and RD (r=-0.34, p<0.0001) of the cingulum, whereas $FA_{0.30}$ (r=0.11, p=0.17) and AD (r=-0.060, p=0.45) did not correlate with ALV. By contrast, of the parameters of the patient groups only volume in mild TBI (r=0.35, p=0.0015) correlated with ALV.

There was a positive correlation (p<0.05) between AD and ALV in mild TBI (r=0.22, p=0.047) but after Bonferroni correction it was not statistically significant.

In the linear model analysis ALV correlated with $MD_{0.30}$ (p=0.0017), FAC (p=0.0036), MDC (p<0.001), and RD (p=0.0019) of controls, whereas there were no correlations between ALV and DTI parameters in the patient group.

5 Discussion

Increased FA values and AD have been reported in patients with hydrocephalus [30, 31]. Further, in a recent study ventricular size correlated negatively with FA and RD of the core of normal cingulum in middle-aged subjects [32]. The present study was designed to evaluate associations between the size of the lateral ventricles and DTI parameters of cingulum in patients with TBI. In our study, DTI parameters were not generally associated with ALV in patients with TBI, whereas ventricular size correlated with most diffusion metrics in control subjects.

We used TBCA [36] to eliminate the contribution of the peripheral branches similarly to previous studies of cingulum [32, 36]. Based on our tractography technique the whole core of the cingulum excluding parahippocampal cingulum and occipital branches, was analyzed. We did not divide cingulum into parts, as in some previous studies [32, 36, 37]. Cross-sectional areas of the body of the lateral ventricles were used instead of volumes of the whole lateral ventricles, because the shape and morphology of the core of cingulum can be assumed to be influenced more by the size of the body than the size of the other parts of the ventricles. Our study included patients in the post-acute phase with a marked range in time from injury, which is a possible limitation, since dynamic changes in DTI metrics have been shown to occur over time [24, 27, 35, 38].

A growing scientific literature has used DTI to examine WM pathology in patients with TBI. Decreased FA can be considered to be a sign of a variety of pathologic processes, such as damage to myelin or axon membranes, reduced axonal integrity, or increased edema. Among patients with post-acute TBI, decreased FA and/or increased MD value is a constant finding in several areas of the brain in patients and in all severities of TBI, but the findings are not always completely unequivocal especially in mild TBI [38]. Alterations in AD tend to be linked to pathology involving axons, whereas changes in RD are commonly associated with destruction of myelin. Some studies have reported increased AD [27, 38] and others have found decreased AD [24] after TBI compared to healthy subjects. In previously published longitudinal analysis, the findings on the evolution of DTI metrics over time are also partly inconsistent. Perez et al. observed a decrease in AD with a reduction of FA [27] whereas some other investigators have reported an increase in AD and FA [24, 35] over time from acute or subacute to chronic phase. RD seems to increase or remain elevated over time especially in moderate and severe TBI [6, 24, 27, 38]. The elevation of MDC and RD with a decrease in FA are possibly due to myelin damage, which compromises water

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diffusion in the predominant direction along the axis of WM bundles and causes greater diffusion perpendicular to axons [6]. Our results are mainly consistent with the literature. In our patients, RD and MD were increased in moderate to severe TBI but not in mild TBI, whereas there were no significant changes in AD.

It has been commonly argued that RD and MD increase and FA values decrease with aging [39]. A previous study has reported that RD and MD values decrease, and FA values increase in the core of the superior cingulum because of age-dependent ventricular enlargement in middle-aged subjects [32]. Additionally, some studies have reported increased FA and AD in patients with hydrocephalus. This phenomenon has been suggested to be related to stretching of the axons and packing of axons that lead to diminished extracellular spaces. [30, 31, 40, 41] Our aim was to study whether the same phenomenon is also true for patients with TBI, since ventriculomegaly is a frequent finding after TBI. [42, 43] The outcome of the current study was mainly consistent with the hypothesis. In our study, the mean size of lateral ventricles of both patient groups separately differed significantly from that of control group. It can be assumed that TBI-related widening of lateral ventricles can have a reverse effect on the DTI metrics of the tracts proximal to the lateral ventricles, and lead to masking of TBI-related pathological changes in white matter studied with DTI. This phenomenon may lead to conflicting results when relying only on group mean comparisons.

Both atrophy and diffusivity changes are commonly found in chronic TBI, and they have been reported to correlate with severity of TBI [18–22, 33–35]. Thus, it could be supposed that atrophy measures and DTI parameters would correlate with each other. However, our study showed the lack of correlations between diffusivity of cingulum and central atrophy. This can be related to the opposite effects of tract injury increasing radial diffusivity and ventricular enlargement decreasing radial diffusivity in cingulum. Further, it is obvious that ventricular enlargement can mask or decrease DTI abnormalities of cingulum. Our results suggest that the variability of the size of lateral ventricles could be a confounding factor and should be taken into account while using DTI to study the integrity of cingulum both in group comparisons and in individual patients.

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Attachments

Table 1   **Demographics of the study subjects**

	Controls (n=80)	Patients (n=77)
Age (mean±SD,range) (years)	36.3±10.9, 19-56	38.2±10.2, 18-56
Sex (m/w) (n)	40/40	38/39
Cause of injury (traffic/fall/violence/other)		46/12/9/10
Time from TBI (median, range) (months)		42, 3-195
Severity of TBI (mild/moderate/severe)		40/24/13
GOS-E score (mean+SD, range)		5.65±0.86, 4-7

SD Standard deviation, *m* Males, *w* Women, *TBI* Traumatic brain injury, *GOS-E* Glasgow Outcome Scale Extended

Table 2   **Volumes, mean FA, mean MD, and axial and radial diffusivities of cingulum of patients TBI (n=77) and healthy controls (n=80). Results in mean values (standard deviations).**

	Controls	TBI	*p* value
$Vol_{0.30}$ (mL)			
right	6.14 (1.45)	5.37 (1.86)	0.008
left	7.00 (1.67)	6.28 (1.78)	0.011
$FA_{0.30}$ (μm^2/ms)			
right	0.466 (0.013)	0.461 (0.016)	0.064
left	0.477 (0.013)	0.474 (0.015)	0.362
$MD_{0.30}$ (μm^2/ms)			
right	0.787 (0.023)	0.795 (0.023)	0.059
left	0.782 (0.021)	0.789 (0.023)	0.093
FAC (μm^2/ms)			
right	0.525 (0.030)	0.507 (0.038)	0.002
left	0.561 (0.032)	0.545 (0.047)	0.026
MDC (μm^2/ms)			
right	0.788 (0.025)	0.796 (0.024)	0.082
left	0.785 (0.021)	0.791 (0.024)	0.192
AD (μm^2/ms)			
right	1.295 (0.041)	1.286 (0.054)	0.48
left	1.343 (0.047)	1.332 (0.060)	0.40
RD (μm^2/ms)			
right	0.535 (0.031)	0.552 (0.034)	0.0022
left	0.507 (0.029)	0.522 (0.042)	0.0189

TBI Traumatic brain injury *FA* fractional anisotropy, *MD* Mean diffusivity, *TBI* Traumatic brain injury, *Vol_{30}* mean volume at threshold 0.30, *FAC* Fractional anisotropy of the core of cingulum, *MDC* Mean diffusivity of the core of cingulum, *AD* Axial diffusivity, *RD* Radial diffusivity

Table 3   Mean size of lateral ventricles of control group (n=80) and the patient group (n=77). Results in mean values (standard deviations).

	Controls	Patients	*p* value
Size (mm²) right left	 80.6 (37.3) 91.6 (46.6)	 114.6 (63.5) 126.0 (74.0)	 0.0001 0.001
TBI Traumatic brain injury			

Table 4   The correlation between the size of lateral ventricles and DTI parameters, volume of cingulum and age. Results in Pearson's correlation coefficients (p-value).

	Controls	Patients (mTBI)	Patients (M/STBI)
Age	0.26 (0.0009)	0.057 (0.62)	0.41 (0.00023)
Volume (mL)	0.33 (< 0.0001)	0.35 (0.0015)	-0.12 (0.32)
FA$_{0.30}$ (µm²/ms)	0.11 (0.17)	0.074 (0.51)	-0.12 (0.32)
MD$_{0.30}$ (µm²/ms)	-0.29 (0.0003)	0.078 (0.49)	-0.019 (0.87)
FAC (µm²/ms)	0.29 (0.0002)	0.17 (0.13)	-0.12 (0.31)
MDC (µm²/ms)	-0.36 (< 0.0001)	0.076 (0.50)	-0.073 (0.51)
AD (µm²/ms)	-0.060 (0.45)	0.22 (0.047)	-0.22 (0.060)
RD (µm²/ms)	-0.34 (< 0.0001)	-0.11 (0.35)	0.095 (0.42)

mTBI Mild TBI, *M/STBI* Moderate to severe TBI, *TBI* Traumatic brain injury, *FA* fractional anisotropy, *MD* Mean diffusivity, *Vol$_{30}$* mean volume at threshold 0.30, *FAC* Fractional anisotropy of the core of cingulum, *MDC* Mean diffusivity of the core of cingulum, *AD* Axial diffusivity, *RD* Radial diffusivity
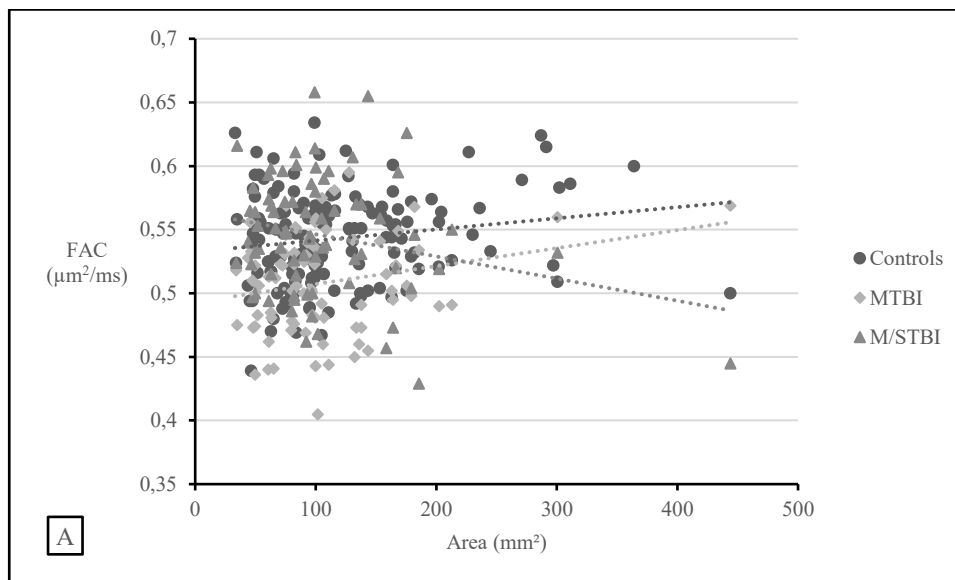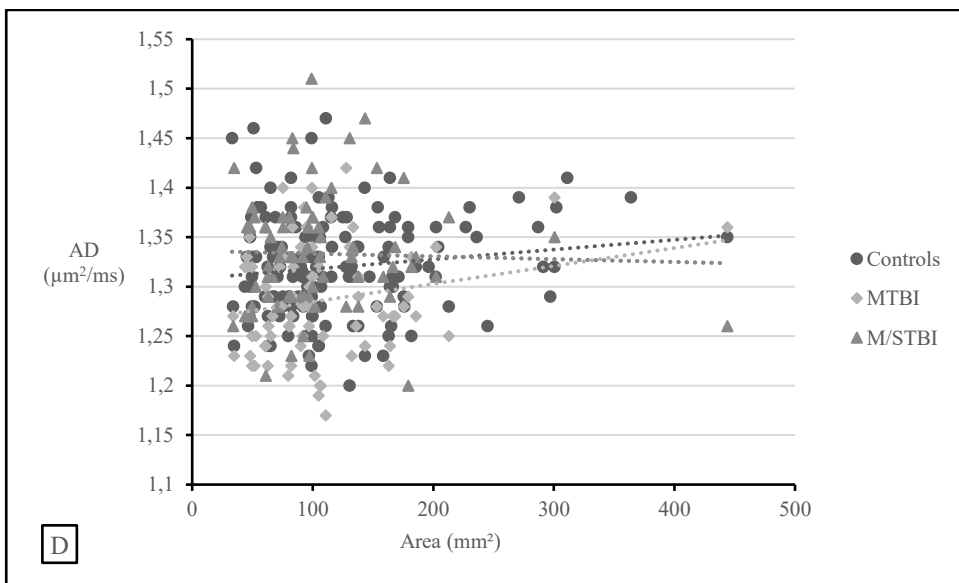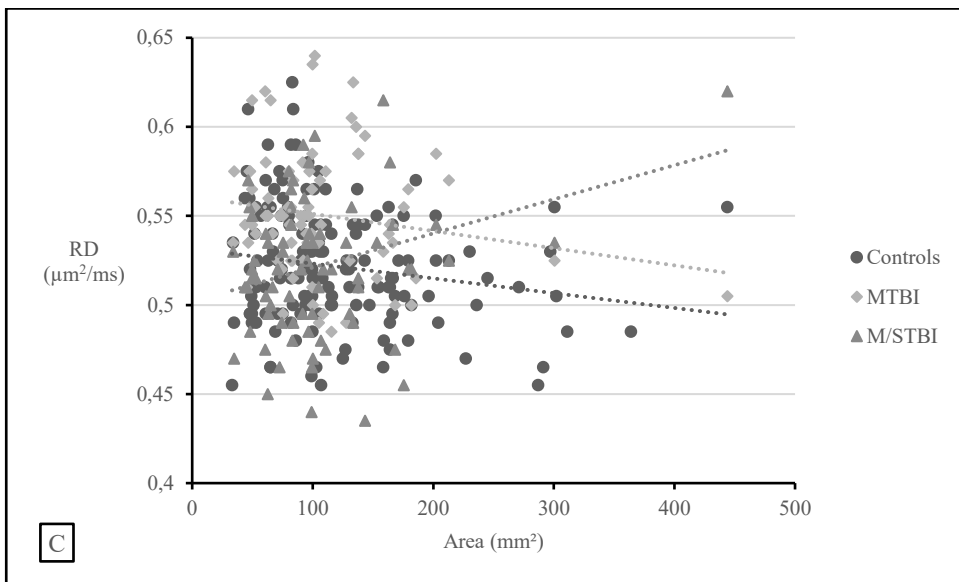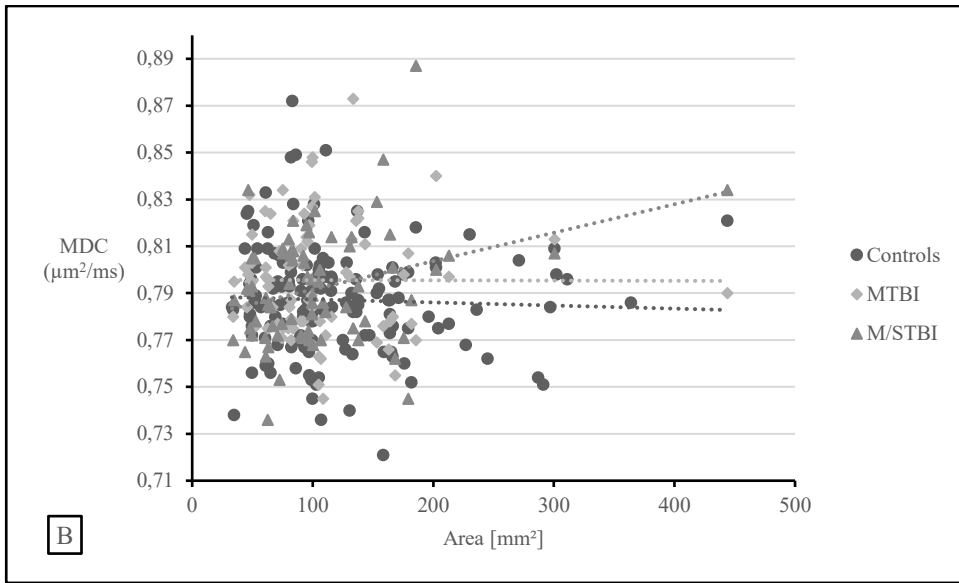
Fig. 1 The relationship of the cross-sectional area of lateral ventricles and core parameters of cingulum (FAC, MDC, AD and RD) in mild TBI, moderate and severe TBI and control group. A FA values (μm^2/ms), B Mean diffusivity (μm^2/ms), C Radial diffusivity (μm^2/ms), and D Axial diffusivity (μm^2/ms)